UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/091,605	06/16/98	BORTS	T X-9872

EXAMINER

LEE,G

HM22/0316

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ART UNIT	PAPER NUMBER
1632	5

DATE MAILED: 03/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/091,605	Borts et al
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-18 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-18 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Specification

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

Claim Objections

Claims 14-15 are objected to under 37 CFR 1.75(c) as being in improper form because claims 14-15 are dependent on claims which are themselves multiple dependent claims. See MPEP § 608.01(n). Furthermore, claims 14 and 15 are drawn to a cell line and a vector, respectively, while claims 1-12, from which claims 14 and 15 depend, are drawn to a method. For the purpose of compact prosecution, however, claims 14 and 15 will be treated as claiming a cell line and vector, respectively, that are used in the method of claim 1 only.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The factors to be considered for enablement of an invention have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth

of the claims. *Ex Parte Forman*, (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-13 and 16 are drawn to a method of treating Type I or Type II diabetes utilizing ex vivo gene therapy comprising administration of cell lines transformed with a vector comprising a promoter driving expression of a DNA sequence encoding glucagon like proteins, and compositions for performing the same.

The claims are not enabled as the specification does not provide guidance as to the dosage amounts, dosage frequencies, modes of delivery, appropriate expression levels and targeting to supply therapeutic treatment to diabetes or predictably without undue experimentation such that one could induce treatment to any and all Type I or Type II diabetes. While applicants description teaches the skilled artisan how to make the claimed compositions, the description fails to provide guidance to the skilled artisan on how to use the claimed compositions for carrying out the claimed methods of gene therapy. In particular, no protocol is described in the specification comprising administration of cells transformed with a vector comprising a promoter and DNA expressing glucagon like proteins for treatment of the instant invention. Pages 11-22, of the specification, teach the description to the construction of the vector encoding GLP-1 protein of pGT-h+tLB+GLP-1 and pGT-h+tLB+Val8GLP-1. The specification contemplates a number of well known methods that exist for introducing the genetic material into target cells but the specification does not provide any teaching or evidence for therapy. The specification does not provide sufficient guidance as to the appropriate route of administration of the cells or

vectors for treating diabetes or the appropriate concentration of cells or vectors for any treatment of that one of ordinary skill in the art could reproducibly and consistently effectively treat the patient in need thereof without undue experimentation.

Although the concept of gene therapy has potential, the realities of the parameters which will result in therapeutic benefit have not been achieved. With regard to *in vivo* transfection of the claim-designated vectors, the specification provides no example or therapeutic methodology that would encompass claim 13. The achievement of therapeutic results by gene therapy, the art as a whole found this to be unpredictable. Blau et al. stated that the main challenge in gene therapy is the achievement of efficient vector delivery and gene expression (Blau et al (1995), page 1204, col. 1-2 bridg. Sent. And page 1205, col. 1-2 bridg. Sent.). Crystal (1995) stated that human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy (abstract) and that the human transfers had been plagued with inconsistent results (page 409, col.1, parag. 2, lines 1-4). Miller et al (1995) that before gene therapy is an option for treating genetic diseases, there is a requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells either in vivo or ex vivo accurately and efficiently (page 190, col. 1, parag. 1, lines 1-7). Verma et al (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy (page 239, col. 3, parag. 1.). Ross et al (1996) state that the technical impediment to gene transfer (as a therapy) is the lack of vector systems, and that unless it is possible to deliver the gene to the appropriate blood

or body cells and in sufficient quantities, gene therapy will not be efficacious (page 1782, col. 2, parag. 1, lines 1-4). Moreover, in the "Report and Recommendations of the Panel to Asses the NIH Investment in Research on Gene Therapy" (published December 7, 1995), Orkin and Motulsky indicate that clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol; that major difficulties of gene therapy include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host; that it is not always possible to extrapolated directly from animal experiments to human studies; and that while the most straight-forward application of gene therapy may be in the treatment of single-gene inherited disorders, practical difficulties need to be address, i.e. delivery of the appropriate gene to a specific cell type or tissue, gaining access to the relevant cell type for correction of the defect, assessing the total fraction of cells in a tissue that need to be corrected, achieving the level of expression required for correction, and regulating expression of the added gene once it is transferred into appropriate target cells (see, e.g. pages 1 and 2, points 2,3, and 5, for example, page 5, under "Single-gene inherited disorders", and page 14, bullet parag. 3-6).

Another issue is the relevant animal models which is supported by the teachings of Orkin et al (p. 10 and 13). Orkin stress the importance of using relevant animal models for determining the effectiveness of therapeutic methodologies. Applicants description does not provide any evidence that animal models available to the skilled artisan would provide a reasonable nexus to that of human diabetes. The specification on page 22 teaches transformed 293 cells were

surgically transplanted under the kidney capsule of 8 week old Zucker Diabetic Fatty male rats by administering with a 23 gauge blunt needle (lines 19-28). No results on the effectiveness of this implant would have on the rat or the implication toward the treatment of human diabetes.

With regard to *ex vivo* gene therapy strategies from treating diseases, the specification is non-enabling as the specification does not provide sufficient guidance as to how one of ordinary skill in the art would treat a patient having the disclosed diseases by administering genetically altered cell. The specification does not teach any methodology associated with such treatment regimen including the number of cells to be administered, the route of administration, or the relevant cell therapy target site for treating diabetes. Moreover, the state of the art at the time of filing suggests that cell transplantation therapies to treat any diseases or disorders are neither routine nor predictable. Ledley, F (1996) in a review of "Pharmaceutical Approach to Somatic Gene Therapy", states that several factors limit the clinical potential of cell-based approaches to gene therapy. First, the cultivation, genetic manipulation, quality control and transplantation of autologous cells is expensive relative to the cost of a conventional pharmaceutical or biological product. Second, there is little clinical experience in cellular transplantation of cells other than bone marrow progenitors and , to a lesser extent, epidermis (p. 1596, col. 2, parag. 2). As to the achievement of treating diabetes using the methods of the instant invention, the art as a whole found this to be unpredictable of the glucagon like proteins efficacy on the treatment of diabetes. Holst et al (1998) state that because of rapid and extensive metabolization, the peptide is not immediately clinically applicable and , as a therapeutic principle, GLP-1 is still in its infancy (p.

336, abstract). Haak, T (1999) teaches that unfortunately, the idea the GLP-1 is superior to all other currently available antidiabetic substances, except insulin, is clouded by the extremely short half-life of less than 2 minutes *in vivo* and that intensive research in the interesting field of the potential therapeutic application of glucagon-like peptide action suggests that answers to many of the unsolved problems will soon be forthcoming (p. S111, col. 1, parag. 1).

Furthermore, the description fails to provide any working examples which demonstrate any therapeutic advantage of the claimed methods. Therefore, it would have required undue experimentation for the skilled artisan to practice the claimed invention in light of the unpredictability of gene therapy, the lack of teachings for parameters to practice the claimed invention in the description, the absence of working examples in the description, the absence of teachings in the art, and the breadth of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 16 contain the terms "immunologically isolated", but there is no definition of these terms in the specification. The words "immunologically isolated" are vague and indefinite such that the metes and bounds of the claims can not be readily established as to what would be entailed or how is the isolation accomplished from the mammal's immune system?

Claims 1 and 16 are vague and indefinite for the recitation of "and", ~~is an improper Markush language~~. Changing "and" to "or" will overcome this rejection.

Claim 10 are vague and indefinite for the recitation of "or" is an improper Markush language. Changing "or" to "and" will overcome this rejection.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim in its "substantially as hereinbefore described with reference to any one of the examples".

Claim 18 is vague and indefinite in its recitation of " capable of " because the specification does not define those factors which make the cells expressible or not expressible. Applicant should delete capable of.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-15 and 17-18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hilliker et al (WO 90/01540).

Hilliker et al teach a method for stabilizing heterologous protein expression and vectors for use with chloramphenicol acetyl transferase (CAT) gene fused in frame with a gene encoding a heterologous protein (abstract). Hilliker et al further teach a plasmid pCGLP139 expresses a CAT-GLP-1 hybrid protein under the control of the E. coli trp promoter-operator (page 25, line 22-23). The plasmid was used to transform E. coli W3110 to ampicillin resistance and one colony was grown in culture overnight in complete M9 medium. After lysing the cells, CAT(1-73)-GLP-I(7-37) hybrid protein was observed and analyzed. Thus, Hilliker et al anticipate claims 14-15 and 17-18 of the instant invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
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